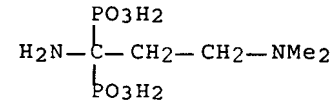
ACCESSION NUMBER: 1998:130639 CAPLUS Full-text
DOCUMENT NUMBER: 128:228387
TITLE: Differential effects of aminosubstituted analogs of hydroxy bisphosphonates on the growth of Dictyostelium discoideum
AUTHOR(S): Brown, R. J.; Van Beek, E.; Watts, D. J.; Lowik, C. W. G. M.; Papapoulos, S. E.
CORPORATE SOURCE: Department of Molecular Biology and Biotechnology, University of Sheffield, Sheffield, UK
SOURCE: Journal of Bone and Mineral Research (1998), 13(2), 253-258
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Replacing the hydroxyl group in the bone-binding site of three clin. useful bisphosphonates (etidronate, pamidronate, and olpadronate) by an amino group resulted in great differences in their antiresorptive potencies in vitro. In the present study, this is also shown in vivo in mice treated with the six bisphosphonates at doses of up to 16 μM/kg/day for 12 days. Because binding to bone mineral is nearly the same for all tested bisphosphonates, these findings suggest that the aminosubstitution affects the cellular action of the bisphosphonates. This was tested in the cellular slime mold Dictyostelium discoideum in which cellular effects of bisphosphonates can be examined independently of binding to bone mineral. Etidronate and its aminosubstituted analog were equipotent in inhibiting amebal growth, while pamidronate was somewhat more potent than its analog. Whereas olpadronate was a potent inhibitor of axenic growth of Dictyostelium amebae, the aminosubstitution reduced its potency drastically (IC50 12 μM and 700 μM, resp.). The similarities between the inhibitory effects of the bisphosphonates tested on bone resorption in vitro and in vivo and on the growth of Dictyostelium amebae confirm that the differences in antiresorptive potencies found reflect differences in cellular effects and suggest that bisphosphonates may bind to more than one intracellular target.

IT 63132-38-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(differential effects of amino-substituted analogs of hydroxy bisphosphonates on growth of Dictyostelium discoideum)

RN 63132-38-7 CAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:132766 CAPLUS Full-text
DOCUMENT NUMBER: 126:144414
TITLE: Amino-substituted bisphosphonic acids
INVENTOR(S): Papapoulos, Socrates; Van Beek, E. R.;

Lowick, C. W. G. M.; Labriola, Rafael; Vecchioli, Adriana
PATENT ASSIGNEE(S): Gador S.A., Argent.; University of Leiden
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

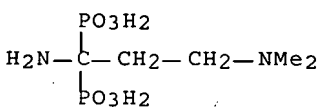
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 753523	A1	19970115	EP 1995-110706	19950710
R: GB				
WO 9702827	A1	19970130	WO 1996-EP2981	19960708
W: AU, BR, CA, CN, CZ, FI, IL, JP, KP, KR, NO, PL, RU, SK, US, VN				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9666125	A	19970210	AU 1996-66125	19960708
EP 837682	A1	19980429	EP 1996-925679	19960708
EP 837682	B1	20021106		
R: DE, FR, GB, NL				
JP 11508905	T	19990803	JP 1996-505494	19960708
ZA 9605798	A	19980109	ZA 1996-5798	19960709
US 5990098	A	19991123	US 1998-983247	19980901

PRIORITY APPLN. INFO.: EP 1995-110706 A 19950710
WO 1996-EP2981 W 19960708
OTHER SOURCE(S): MARPAT 126:144414

AB 1-Aminoalkylidene-1,1-bisphosphonic acids, RC(NH2)[P(O)(OH)2]2 (R = C1-9 straight-chain or branched aliphatic hydrocarbon radical which is optionally substituted by one or more amino or aminoalkyl groups with the exception of a terminal aminoalkyl group NR1R2; R1 = C1-9 straight-chain or branched, saturated or unsatd. aliphatic hydrocarbon radical, R2 = cyclohexyl or cyclohexylmethyl, benzyl or a straight-chain or branched, C4-18 saturated or unsatd. aliphatic hydrocarbon radical, as a single substituent of R) or any salts thereof, useful for treatment of disorders of calcium and bone metabolism, is described. Thus, hydrolysis of PCl3 gave phosphorus acid which on treatment with MeCN in MeOH followed by acidic workup gave 100% MeC(NH2)[P(O)(OH)2]2. Some binding of compds. prepared with bone materials is described.

IT 63132-38-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and bone binding activity of amino-substituted bisphosphonic acids)

RN 63132-38-7 CAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)

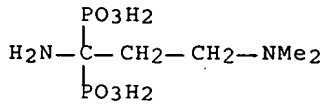


L38 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:642672 CAPLUS Full-text
DOCUMENT NUMBER: 125:316217
TITLE: Dissociation of binding and antiresorptive properties of hydroxybisphosphonates by substitution of the hydroxyl with an amino group
AUTHOR(S): Van Beek, Ermond; Lowik, Clemens; Que, Ivo; Papapoulos, Socrates
CORPORATE SOURCE: Department Endocrinology and Metabolic Diseases, University Hospital, Leiden, Neth.
SOURCE: Journal of Bone and Mineral Research (1996), 11(10), 1492-1497
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of this study was to examine the role of the R1 moiety of bisphosphonates in binding to bone mineral and for antiresorptive action. For this, the R1 chain of three clin. useful hydroxybisphosphonates (etidronate, pamidronate, and olpadronate) was substituted with an amino group. The effects of the amino-substituted bisphosphonates were compared with those of their hydroxy counterparts in a crystal growth assay and in fetal mouse long bone cultures which are representative of bisphosphonate actions in vivo. It was found that all three amino-substituted compds. and their hydroxy analogs bound with similar affinity to bone mineral and inhibited the growth of calcium oxalate crystals to the same extent. Surprisingly, the antiresorptive effect of olpadronate was totally abolished by the amino substitution of the hydroxyl group while that of pamidronate was reduced by about six-fold and that of etidronate did not change. These studies demonstrate the involvement of the entire bisphosphonate mol. in the cellular mechanism of antiresorptive action. In addition, the amino-substituted analog of olpadronate, which lacks any antiresorptive action but retains all other properties of olpadronate, provides an excellent tool for the study of specific cellular effects involved in bisphosphonate action.

IT 63132-38-7
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(dissociation of bone mineral binding and antiresorptive properties of hydroxybisphosphonates by substitution of hydroxyl with amino group)
RN 63132-38-7 CAPLUS
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)



L38 ANSWER 11 OF 11 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:432676 BIOSIS Full-text
DOCUMENT NUMBER: PREV199900432676
TITLE: Differential effects of olpadronate and its aminosubstituted analog IG-9402 on the regulation of cytosolic calcium in cultured rat osteoblasts.
AUTHOR(S): Vazquez, G. [Reprint author]; Boland, R.

[Reprint author]; Roldan, E.; Perez-Lloret, A.
CORPORATE SOURCE: Dept. Biologia, Bioquimica and Farmacia, Universidad Nacional del Sur, Bahia Blanca, Argentina
SOURCE: Journal of Bone and Mineral Research, (Sept., 1999) Vol. 14, No. SUPPL. 1, pp. S239. print.
Meeting Info.: Twenty-First Annual Meeting of the American Society for Bone and Mineral Research. St. Louis, Missouri, USA. September 30-October 4, 1999. American Society for Bone and Mineral Research.
CODEN: JBMREJ. ISSN: 0884-0431.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Oct 1999
Last Updated on STN: 3 May 2000

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L13             3 SEA FILE=REGISTRY ABB=ON  (L11 OR L12)


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L13  ANSWER 1 OF 3  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   586348-26-7  REGISTRY
ED   Entered STN:  16 Sep 2003
CN   Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis-, nitrate (9CI)
     (CA INDEX NAME)
MF   C5 H16 N2 O6 P2 . x H N O3
SR   CA
LC   STN Files:   CA, CAPLUS, TOXCENTER

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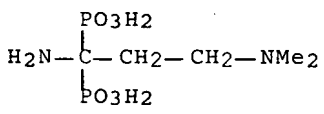

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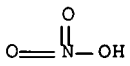
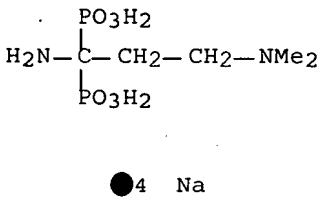


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L13 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2007 ACS on STN
RN 373645-02-4 REGISTRY
ED Entered STN: 05 Dec 2001
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis-, tetrasodium salt (9CI) (CA INDEX NAME)
MF C5 H16 N2 O6 P2 . 4 Na
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL
CRN (63132-38-7)



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L13 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2007 ACS on STN
RN 63132-38-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN Phosphonic acid, P,P'-[1-amino-3-(dimethylamino)propylidene]bis- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [1-amino-3-(dimethylamino)propylidene]bis- (9CI)
OTHER NAMES:
CN IG 9402
CN Lidadronic acid
MF C5 H16 N2 O6 P2
CI COM
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, DDFU, DRUGU, IFICDB, IFIPAT, IFIUDB, PHAR, TOXCENTER, USAN, USPAT2, USPATFULL
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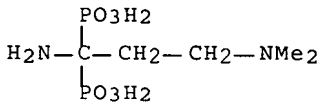

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22 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
22 REFERENCES IN FILE CAPLUS (1907 TO DATE)

STRUCTURE SEARCH

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L13 3 SEA FILE=REGISTRY ABB=ON (L11 OR L12)
L22 24 SEA FILE=CAPLUS ABB=ON L13

L39 14 L22 NOT L23

FILE 'BIOSIS' ENTERED AT 15:32:32 ON 05 SEP 2007

FILE COVERS 1926 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1926 TO DATE.

RECORDS LAST ADDED: 29 August 2007 (20070829/ED)

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L12 2 SEA FILE=REGISTRY ABB=ON 63132-38-7/CRN
L13 3 SEA FILE=REGISTRY ABB=ON (L11 OR L12)
L29 2 SEA FILE=BIOSIS ABB=ON L13

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L40           0 L29 NOT L30


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FILE RELOADED January 2007
FILE LAST UPDATED:  Sep 3, 2007 (20070903/ED)

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L20           1 SEA FILE=REGISTRY ABB=ON  63132-38-7/RN
L21           1 SEA FILE=PHAR ABB=ON  L20


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DUPLICATE IS NOT AVAILABLE IN 'PHAR'.
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PROCESSING COMPLETED FOR L21
L41           15 DUP REM L39 L21 (0 DUPLICATES REMOVED)
                 ANSWERS '1-14' FROM FILE CAPLUS
                 ANSWER '15' FROM FILE PHAR

=> d ibib abs hitind 1-14; d all 15; fil hom

L41  ANSWER 1 OF 15  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2006:818726  CAPLUS  Full-text
DOCUMENT NUMBER:          146:288334
TITLE:                    Dissociation of the pro-apoptotic effects of
                          bisphosphonates on osteoclasts from their
                          anti-apoptotic effects on osteoblasts/osteocytes with
                          novel analogs
AUTHOR(S):                Plotkin, Lilian I.; Manolagas, Stavros C.; Bellido,
```

Teresita
CORPORATE SOURCE: Division of Endocrinology and Metabolism, The Center for Osteoporosis and Metabolic Bone Diseases, The Central Arkansas Veterans Healthcare System, University of Arkansas for Medical Sciences, Little Rock, AR, 72205, USA
SOURCE: Bone (San Diego, CA, United States) (2006), 39(3), 443-452
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bisphosphonates induce osteoclast apoptosis, thereby decreasing bone resorption and reducing the rate of bone remodeling. Earlier work from our group and others has demonstrated that, addnl., bisphosphonates prevent osteoblast and osteocyte apoptosis in vivo and in vitro, raising the possibility that perhaps part of their anti-fracture efficacy may result from preserving the integrity of the osteocyte network and prolonging the working time of bone forming cells. Whereas induction of osteoclast apoptosis results from inhibition of the mevalonate pathway or from conversion to toxic ATP analogs, prevention of osteoblastic cell apoptosis is mediated by connexin43 hemichannel opening and activation of the extracellular signal-regulated kinases (ERKs). We examined here the ability of several bisphosphonates, including novel analogs, to exert these two effects. All 16 bisphosphonates studied inhibited etoposide-induced apoptosis of MLO-Y4 osteocytic cells and osteoblastic cells derived from calvaria, with EC50 between 10-12 and 10-10 M. On the other hand, only 10 analogs induced apoptosis of RAW-264.7-cell-derived osteoclasts. Each of the 6 bisphosphonates that lack pro-apoptotic activity in osteoclasts but retain anti-apoptotic activity in osteoblasts and osteocytes has a structural-related analog that is active in both cell types. These findings indicate that the structural prerequisites for the anti-apoptotic effect of bisphosphonates on cells of the osteoblastic lineage are less stringent than the ones required to induce osteoclast apoptosis and confirm that bisphosphonates act on the two cell types by distinct mechanisms. Preservation of osteoblast and osteocyte viability without inducing osteoclast apoptosis by these bisphosphonates analogs opens new possibilities for the treatment of bone fragility in conditions in which a decrease in bone remodeling is not desirable.

CC 1-12 (Pharmacology)
IT 63132-38-7, IG9402
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bisphosphonate analog IG9402 prevented osteoblast and osteocyte apoptosis without affecting mouse osteoclasts)
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:986477 CAPLUS Full-text
DOCUMENT NUMBER: 140:156750
TITLE: Quantitative Structure-Activity Relationships for γδ T Cell Activation by Bisphosphonates
AUTHOR(S): Sanders, John M.; Ghosh, Subhash; Chan, Julian M. W.; Meints, Gary; Wang, Hong; Raker, Amy M.; Song, Yongcheng; Colantino, Alison; Burzynska, Agnieszka; Kafarski, Pawel; Morita, Craig T.; Oldfield, Eric
CORPORATE SOURCE: Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL, 61801, USA
SOURCE: Journal of Medicinal Chemistry (2004), 47(2), 375-384
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:156750

AB γδ T cells are the first line of defense against many infectious organisms and are also involved in tumor cell surveillance and killing. They are stimulated by a broad range of small, phosphorus-containing antigens (phosphoantigens) as well as by the bisphosphonates commonly used in bone resorption therapy, such as pamidronate and risedronate. Here, we report the activation of γδ T cells by a broad range of bisphosphonates and develop a pharmacophore model for γδ T cell activation, in addition to using a comparative mol. similarity index anal. (CoMSIA) approach to make quant. relationships between γδ T cell activation by bisphosphonates and their three-dimensional structures. The CoMSIA analyses yielded R2 values of .apprx.0.8-0.9 and q2 values of .apprx.0.5-0.6 for a training set of 45 compds. Using an external test set, the activities (IC50 values) of 16 compds. were predicted within a factor of 4.5, on average The CoMSIA fields consisted of .apprx.40% hydrophobic, .apprx.40% electrostatic, and .apprx.20% steric interactions. Since bisphosphonates are known to be potent, nanomolar inhibitors of the mevalonate/isoprene pathway enzyme farnesyl pyrophosphate synthase (FPPS), we also compared the pharmacophores for γδ T cell activation with those for FPPS inhibition, using the Catalyst program. The pharmacophores for γδ T cell activation and FPPS inhibition both consisted of two neg. ionizable groups, a pos. charge feature and an endocyclic carbon feature, all having very similar spatial dispositions. In addition, the CoMSIA fields were quite similar to those found for FPPS inhibition by bisphosphonates. The activities of the bisphosphonates in γδ T cell activation were highly correlated with their activities in FPPS inhibition: R = 0.88, p = 0.002, vs. a human recombinant FPPS (N = 9 compds.); R = 0.82, p < 0.0001, for an expressed Leishmania major FPPS (N = 45 compds.). The bisphosphonate γδ T cell activation pharmacophore differs considerably, however, from that reported previously for γδ T cell activation by phosphoantigens (Gossman, W.; Oldfield, E. J. Med. Chemical 2002, 45, 4868-4874), suggesting different primary targets for the two classes of compds. The ability to quite accurately predict the activity of bisphosphonates as γδ T cell activators by using 3D QSAR techniques can be expected to help facilitate the design of addnl. bisphosphonates for potential use in immunotherapy.

CC 1-3 (Pharmacology)

IT 2809-22-5 16559-82-3 32545-64-5 32545-65-6 32545-72-5 32579-17-2
40391-99-9 56152-34-2 56375-74-7 63132-38-7 67242-32-4
70010-75-2 70010-76-3 70010-77-4 70010-79-6 70010-82-1
70010-83-2 70010-87-6 71066-25-6 71066-28-9 71066-29-0
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114119-81-2 118072-93-8, Zometa 121368-58-9, Olpadronate 124351-85-5
124351-86-6 124351-87-7 124369-71-7 129318-43-0, Fosamax
129951-00-4 134579-56-9 149543-15-7 180064-38-4 634612-13-8
634612-14-9 634612-16-1 656238-26-5
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quant. structure-activity relationships for γδ T cell activation by bisphosphonates)

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:652131 CAPLUS Full-text
DOCUMENT NUMBER: 139:214237

TITLE: Preparation of nitrate prodrugs able to release nitric oxide in a controlled and selective way and their use for prevention and treatment of inflammatory, ischemic and proliferative diseases

INVENTOR(S): Scaramuzzino, Giovanni
PATENT ASSIGNEE(S): Italy

SOURCE: Eur. Pat. Appl., 313 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1336602	A1	20030820	EP 2002-425075	20020213
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRIORITY APPLN. INFO.:			EP 2002-425075	20020213

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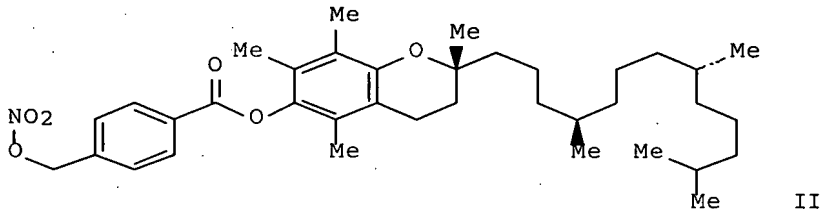

II

AB New pharmaceutical compds. of general formula F-(X)q (I) [q = 1-5, preferably 1; F is chosen among drugs such as δ-tocopherol, clidanac, diethylhomospermine, glucosamine, thymocartin, vofopitant, etc.; X is chosen among 4 groups M, T, V, and Y where M = ONO2, nitrate salt, nitrite ester, ONO, thoinitrite, SNO, etc., T = OR1-M, OR1OR1-M, SR1NR2R1-M, NR2R1-M, NR2R1SR1-M, etc., R1 = saturated or unsatd., linear or branched alkylene, having 1 to 21 carbon atoms or a saturated or unsatd., optionally heterosubstituted or branched cycloalkylene, having 3 to 7 carbon atoms or an optionally heterosubstituted arylene having 3 to 7 carbon atoms; R2 = H, saturated or unsatd., linear or branched 1-21 carbon atom alkyl, saturated or unsatd. optionally heterosubstituted or branched 3-7 carbon cycloalkyl, optionally heterosubstituted 3-7 carbon aryl; R1, R2 = OH, SH, F, Cl, Br, OPO3H2, CO2H, etc.; bond between F and T = carboxylic ester, carboxylic amide, glycoside, azo, thioester, sulfonic ester, etc.; V = Z-M2, OZ-M2, NR2Z-M2, R1Z-M2, OR1-M2, OR1Z-M2, M2 = M, R1-M, OR1-M, SR1-M, NR2R1-M; ZM2 = COCH2CH(M2)CH2N+Me3, COCH2CH2COM2, COCH(NHR2)CH2M2, etc.; Y = 4-COC6H4CH2ONO2, O(CH2)4ONO2, COCH(NH2)CH2ONO2, 3-OC6H4CH2ONO2, etc.] were prepared For example, α-tocopherol reacted with 4-HO2CC6H4CH2ONO2 to give the nitroxymethyl derivative II. The compds. of general formula I are nitrate prodrugs which can release nitric oxide in vivo in a controlled and selective way and without hypotensive side effects and for this reason they are useful for the preparation of medicines for prevention and treatment of inflammatory, ischemic, degenerative and proliferative diseases of musculoskeletal, tegumental, respiratory, gastrointestinal, genito-urinary and central nervous systems.

IC ICM C07C205-00

ICS A61K031-00
CC 26-1 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 1, 28, 29, 33, 34, 63
IT 13005-09-9P 96513-33-6P 116539-59-4P 198483-54-4P 257625-98-2P
329976-33-2P 352464-98-3P 398454-56-3P 398460-42-9P 410071-16-8P
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586350-01-8P 586350-02-9P 586350-03-0P 586350-04-1P 586350-05-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of nitrate prodrugs for treating or preventing inflammatory, ischemic, degenerative, and proliferative diseases)
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:539062 CAPLUS Full-text

DOCUMENT NUMBER: 137:226194
TITLE: Highly Potent Geminal Bisphosphonates. From Pamidronate Disodium (Aredia) to Zoledronic Acid (Zometa)
AUTHOR(S): Widler, Leo; Jaeggi, Knut A.; Glatt, Markus; Mueller, Klaus; Bachmann, Rolf; Bisping, Michael; Born, Anne-Ruth; Cortesi, Reto; Guiglia, Gabriela; Jeker, Heidi; Klein, Remy; Ramseier, Ueli; Schmid, Johann; Schreiber, Gerard; Seltenmeyer, Yves; Green, Jonathan R.
CORPORATE SOURCE: Arthritis and Bone Metabolism Therapeutic Area, Novartis Pharma Research, Basel, CH-4002, Switz.
SOURCE: Journal of Medicinal Chemistry (2002), 45(17), 3721-3738
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:226194
AB Bisphosphonates (BPs) are pyrophosphate analogs in which the oxygen in P-O-P has been replaced by a carbon, resulting in a metabolically stable P-C-P structure. Pamidronate (1b, Novartis), a second-generation BP, was the starting point for extensive SAR studies. Small changes of the structure of pamidronate lead to marked improvements of the inhibition of osteoclastic resorption potency. Alendronate (1c, MSD), with an extra methylene group in the N-alkyl chain, and olpadronate (1h, Gador), the N,N-di-Me analog, are about 10 times more potent than pamidronate. Extending one of the N-Me groups of olpadronate to a pentyl substituent leads to ibandronate (1k, Roche, Boehringer-Mannheim), which is the most potent close analog of pamidronate. Even slightly better antiresorptive potency is achieved with derivs. having a Ph group linked via a short aliphatic tether of three to four atoms to nitrogen, the second substituent being preferentially a Me group (e.g., 4g, 4j, 5d, or 5r). The most potent BPs are found in the series containing a heteroarom. moiety (with at least one nitrogen atom), which is linked via a single methylene group to the geminal bisphosphonate unit. Zoledronic acid (6i), the most potent derivative, has an ED50 of 0.07 mg/kg in the TPTX in vivo assay after s.c. administration. It not only shows by far the highest therapeutic ratio when comparing resorption inhibition with undesired inhibition of bone mineralization but also exhibits superior renal tolerability. Zoledronic acid (6i) has thus been selected for clin. development under the registered trade name Zometa. The results of the clin. trials indicate that low doses are both efficacious and safe for the treatment of tumor-induced hypercalcemia, Paget's disease of bone, osteolytic metastases, and postmenopausal osteoporosis.
CC 1-3 (Pharmacology)
IT 29712-30-9P 32545-72-5P 56152-35-3P 63132-38-7P
63132-40-1P 63161-30-8P 66376-36-1P, Alendronate 67242-32-4P
79778-41-9P, Neridronate 86235-67-8P 89732-96-7P 104261-68-9P
114084-78-5P, Ibandronate 114084-82-1P 114119-81-2P 116162-22-2P
116786-78-8P 116786-79-9P 116786-83-5P 116786-85-7P 116786-88-0P
116786-89-1P 116786-90-4P 118054-12-9P 118054-15-2P 118054-16-3P
118054-18-5P 118054-19-6P 118054-20-9P 118054-23-2P 118054-31-2P
118054-32-3P 118054-33-4P 118054-41-4P 118054-42-5P 118054-51-6P
118054-52-7P 118072-93-8P 118694-16-9P 121368-58-9P, Olpadronate
124351-85-5P 124369-71-7P 124369-72-8P 124369-73-9P 124369-77-3P
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129951-00-4P 129951-01-5P 129951-02-6P 131654-39-2P 131654-40-5P
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132423-95-1P 132423-96-2P 132423-97-3P 132423-98-4P 132423-99-5P

132424-00-1P 132424-01-2P 134579-54-7P 134579-55-8P 134579-56-9P
136671-90-4P 142830-99-7P 149226-80-2P 154188-60-0P 183446-90-4P
183446-98-2P 209002-31-3P 209002-32-4P 459870-45-2P 459870-46-3P
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459870-52-1P 459870-53-2P 459870-54-3P 459870-55-4P 459870-56-5P
459870-57-6P 459870-58-7P 459870-59-8P 459870-60-1P 459870-61-2P
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(bisphosphonates preparation and structure-related bone antiresorptive properties)

REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:833023 CAPLUS Full-text
DOCUMENT NUMBER: 135:376738
TITLE: Compounds and methods for modulating cerebral amyloid angiopathy using inhibitors of an amyloid β peptide
INVENTOR(S): Green, Allan M.; Gervais, Francine
PATENT ASSIGNEE(S): Neurochem, Inc., Can.
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2001085093	A2	20011115	WO 2000-IB2078		20001222
WO 2001085093	A3	20020829			
WO 2001085093	A9	20020926			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2395314	A1	20011115	CA 2000-2395314		20001222
AU 200184313	A	20011120	AU 2001-84313		20001222
EP 1251837	A2	20021030	EP 2000-993855		20001222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
BR 2000016652	A	20021119	BR 2000-16652		20001222
US 2003003141	A1	20030102	US 2000-747408		20001222
US 6670399	B2	20031230			
JP 2003532656	T	20031105	JP 2001-581748		20001222
MX 2002PA06196	A	20021209	MX 2002-PA6196		20020621
AU 2006201445	A1	20060504	AU 2006-201445		20060406
PRIORITY APPLN. INFO.:			US 1999-171877P	P	19991223
			AU 2001-84313	A3	20001222
			WO 2000-IB2078	W	20001222

OTHER SOURCE(S): MARPAT 135:376738
AB The invention provides methods of inhibiting cerebral amyloid angiopathy (CAA) and treating a disease state characterized by cerebral amyloid angiopathy,

e.g., Alzheimer's disease, in a subject using an inhibitor of the 39-40 amino acid amyloid β peptide (Aβ40). The Aβ40 inhibitor is selected from, e.g., sulfonic acid derivs., such as ethanesulfonic acid, 1,2-ethanedisulfonic acid, 1-propanesulfonic acid, 1,3-propanedisulfonic acid, 1,4-butanedisulfonic acid, 1,5-pentanedisulfonic acid, 2-aminoethanesulfonic acid, 4-hydroxy-1-butanesulfonic acid, 1-butanesulfonic acid, 1-decanesulfonic acid, 2-propanesulfonic acid, 3-pentanesulfonic acid, 4-heptanesulfonic acid, etc., and pharmaceutically acceptable salts thereof or from from phosphonic acid derivs., such as diethylphosphonoacetic acid, phenylphosphonic acid, 3-aminopropylphosphonic acid, propylphosphonic acid, etc. The compds. are formulated in a dispersion system, a liposome formulation, or microspheres using a polymeric matrix. The polymeric matrix is selected from natural polymers, such as albumin, alginate, cellulose derivs., collagen, fibrin, gelatin, and polysaccharides, or synthetic polymers such as polyesters, polyethylene glycol, poloxamers, and polyanhydrides. For example, the ability of compds. of the invention to inhibit CAA was measured in 9 wk old hAPP transgenic mice treated with two different concns. of a compound of the present invention, 3-amino-1-propanesulfonic acid sodium salt, 100 and 30 mg/kg. Mice were administered the compound for 8 wk, after which they were sacrificed and their brains were perfused and processed for histol. staining with Thioflavin S. This method may also be used as a screening method for determining activity of a candidate compound for inhibiting CAA. The extent of CAA in brain sections obtained from these animals was qual. determined following staining. The results indicate that the test compound was effective in (i) reducing the number of mice showing CAA, and (ii) showing an effect on the severity of the deposition seen in the brain vasculature of these animals.

IC ICM A61K

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

IT 81-08-3 107-35-7, 2-Aminoethanesulfonic acid 110-04-3, 1,2-Ethanedisulfonic acid 116-63-2 149-45-1 288-94-8, 1H-Tetrazole 594-45-6, Ethanesulfonic acid 831-59-4 860-22-0 926-39-6 993-13-5, Methylphosphonic acid 1068-21-9, Diethyl phosphoramidate 1071-83-6, N-Phosphonomethylglycine 1120-71-4 1132-61-2, 4-Morpholinepropanesulfonic acid 1135-40-6 1571-33-1, Phenylphosphonic acid 1633-83-6 2386-47-2, 1-Butanesulfonic acid 2386-54-1 3095-95-2, Diethylphosphonoacetic acid 3687-18-1, 3-Amino-1-propanesulfonic acid 4408-78-0, Phosphonoacetic acid 4426-50-0 4672-38-2, Propylphosphonic acid 4923-84-6 5117-07-7 5284-66-2, 1-Propanesulfonic acid 5399-58-6 5652-28-8 5994-73-0 6779-09-5, Ethylphosphonic acid 7365-45-9 13138-33-5, 3-Aminopropylphosphonic acid 13419-61-9 13991-98-5, 14047-23-5, (1-Aminopropyl)phosphonic acid 14159-48-9, 2-Propanesulfonic acid 14650-46-5 15471-17-7 15763-57-2 18039-42-4 20283-21-0, 1-Decanesulfonic acid 21668-77-9, 1,3-Propanedisulfonic acid 23052-80-4 23052-81-5 25331-57-1 25595-59-9 26978-64-3, 4-Hydroxy-1-butanesulfonic acid 27665-39-0, 1,4-Butanedisulfonic acid 27797-35-9 31465-25-5 34159-44-9 36585-99-6 37810-68-7 38911-09-0 40391-99-9 40465-65-4, N-Phosphonomethylglycine trisodium salt 51224-03-4 51224-04-5 51650-30-7, 3-Pentanesulfonic acid 51762-95-9 53329-36-5 57605-13-7 58849-79-9 60142-96-3 63585-09-1, Phosphonoformic acid trisodium salt 71119-22-7 72217-85-7 73858-58-9 75277-39-3 76326-31-3, 2-Amino-5-phosphonopentanoic acid 78739-01-2, D-(-)-2-Amino-4-phosphonobutanoic acid 79055-67-7 79055-68-8 81338-23-0 81338-24-1, L-(+)-2-Amino-7-phosphonoheptanoic acid 82283-67-8 82283-68-9 82977-27-3 87625-44-3 88246-85-9 91357-22-1 91586-81-1 99107-93-4 101020-77-3, 1,5-Pentanedisulfonic acid 102805-84-5 108084-41-9 112980-83-3 117414-74-1 126253-57-4 126453-07-4 128241-72-5 129318-43-0 131177-53-2 138199-51-6 143018-67-1 145544-51-0 157381-42-5 168977-94-4,

3-Aminopropyl(methyl)phosphinic acid hydrochloride 183278-21-9,
4-Heptanesulfonic acid 183278-22-0 183278-30-0 183278-32-2
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186295-21-6 186295-22-7 188642-79-7 205248-54-0 216367-45-2
216367-47-4 216367-53-2 216367-60-1 216367-67-8 216367-68-9
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373645-08-0 373645-09-1 373645-10-4 373645-11-5 373645-12-6
373645-13-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors of amyloid β peptide for modulating cerebral amyloid angiopathy)

L41 ANSWER 6 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:416728 CAPLUS Full-text
DOCUMENT NUMBER: 135:14356
TITLE: Phosphonate compounds, and preparation thereof, for treating medical disorders
INVENTOR(S): Hostetler, Karl Y.; Beadle, James R.; Kini, Ganesh D.
PATENT ASSIGNEE(S): The Regents of the University of California, San Diego, USA
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001039724	A2	20010607	WO 2000-US33079	20001204
WO 2001039724	A3	20011018		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2393410	A1	20010607	CA 2000-2393410	20001204
AU 200119497	A	20010612	AU 2001-19497	20001204
AU 785355	B2	20070201		
EP 1233770	A2	20020828	EP 2000-982468	20001204
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2000016058	A	20030715	BR 2000-16058	20001204
JP 2004500352	T	20040108	JP 2001-541459	20001204
RU 2258707	C2	20050820	RU 2002-118327	20001204
IN 2002DN00553	A	20040228	IN 2002-DN553	20020531
MX 2002PA05490	A	20040910	MX 2002-PA5490	20020603
US 2004019232	A1	20040129	US 2002-148374	20021106
US 6716825	B2	20040406		
ZA 2002004194	A	20030820	ZA 2002-4194	20021204
US 2004127735	A1	20040701	US 2004-759345	20040115
US 7034014	B2	20060425		
US 2005176673	A1	20050811	US 2005-100882	20050406
US 7094772	B2	20060822		
US 2005182019	A1	20050818	US 2005-101259	20050406
US 7098197	B2	20060829		
US 2006281706	A1	20061214	US 2006-506292	20060817
AU 2006252074	A1	20070118	AU 2006-252074	20061215
US 2007161602	A1	20070712	US 2007-715604	20070307

PRIORITY APPLN. INFO.:

US 1999-168813P	P	19991203
US 2000-205719P	P	20000519
AU 2001-19497	T0	20001204
WO 2000-US33079	W	20001204
US 2002-148374	A1	20021106
US 2004-759345	A1	20040115
US 2005-100882	A1	20050406
US 2006-506292	A1	20060817

OTHER SOURCE(S): MARPAT 135:14356

AB The invention discloses phosphonate compds., compns. containing them, processes for obtaining them, and their use for treating a variety of medical disorders, e.g. osteoporosis and other disorders of bone metabolism, cancer, and viral infections. Preparation of compds. of the invention, e.g. 1-O-hexadecylpropanediol-3-alendronate, is described.

IC ICM A61K

CC 1-12 (Pharmacology)

IT 147-94-4D, Cytosine arabinoside, derivs. 2809-21-4D, derivs. 4291-63-8D, 2-Chlorodeoxyadenosine, derivs. 10596-23-3D, derivs. 13598-36-2D, Phosphonic acid, derivs. 21679-14-1D, Fludarabine, derivs. 30516-87-1D, Azidothymidine, derivs. 38819-10-2D, derivs. 40391-99-9D, derivs. 63132-38-7D, derivs. 66376-36-1D, Alendronate, derivs. 89987-06-4D, Tiludronate, derivs. 95058-81-4D, Gemcitabine, derivs. 105462-24-6D, derivs. 106941-25-7D, Adefovir, derivs. 113852-37-2D, Cidofovir, derivs. 114084-78-5D, Ibandronate, derivs. 121368-58-9D, Olpadronate, derivs. 125946-92-1D, EB-1053, derivs. 127757-45-3D, derivs. 147127-20-6D, Tenofovir, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphonate compds., and preparation thereof, for treating medical disorders)

L41 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:351360 CAPLUS Full-text

DOCUMENT NUMBER: 132:343333
TITLE: Increasing bone strength with selected bisphosphonates
INVENTOR(S): Manolagas, Stavros C.; Bellido, Teresita
PATENT ASSIGNEE(S): The Board of Trustees for the University of Arkansas, USA; Gador S.A.
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000028982	A2	20000525	WO 1999-US27528		19991119
WO 2000028982	A3	20020711			
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
AU 2000015257	A	20000605	AU 2000-15257		19991119
US 6416737	B1	20020709	US 1999-443841		19991119
PRIORITY APPLN. INFO.:			US 1998-109237P	P	19981119
			US 1999-165480P	P	19991115
			WO 1999-US27528	W	19991119

AB The present invention is a method and composition to increase bone strength in a manner that decreases fracture incidence, which may or may not include increasing bone mineral d. ("BMD"). The invention includes administering an effective amount of a bisphosphonate to a host in need thereof to increase bone strength, which inhibits the apoptosis of osteoblasts and osteocytes, without a significant effect on osteoclasts. In one embodiment, the bisphosphonate is not 1-amino-3-(N,N-dimethylamino)- propyliden-1,1-bisphosphonic acid or its pharmaceutically acceptable salt. An increase in osteoblast life span can lead to an increase in bone mass, i.e., an anabolic effect. Preservation of osteocyte life span can increase bone strength, which may be disproportional to the increase in bone mass. Pretreatment of osteocytes with bisphosphonates for 1h before the addition of 10-6 M dexamethasone inhibited glucocorticoid-induced apoptosis, with minimal effective concentration between 10-9-10-8 M.

IC ICM A61K031-00
CC 1-10 (Pharmacology)
Section cross-reference(s): 63
IT 1406-16-2, Vitamin d 13598-36-2D, Phosphonic acid, alkylidenebis-derivs. 32222-06-3, Calcitriol 40391-99-9 63132-38-7, IG 9402 63132-38-7D, IG 9402, salts 66376-36-1, Alendronate 121368-58-9, Olpadronate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(increasing bone strength with selected bisphosphonates)

L41 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:738897 CAPLUS Full-text
DOCUMENT NUMBER: 132:59109
TITLE: Prevention of osteocyte and osteoblast apoptosis by

bisphosphonates and calcitonin
AUTHOR(S): Plotkin, Lilian I.; Weinstein, Robert S.; Parfitt, A. Michael; Roberson, Paula K.; Manolagas, Stavros C.; Bellido, Teresita
CORPORATE SOURCE: Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Diseases, University of Arkansas for Medical Sciences, Little Rock, AR, 72205, USA
SOURCE: Journal of Clinical Investigation (1999), 104(10), 1363-1374
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Glucocorticoid-induced osteoporosis may be due, in part, to increased apoptosis of osteocytes and osteoblasts, and bisphosphonates (BPs) are effective in the management of this condition. We have tested the hypothesis that BPs suppress apoptosis in these cell types. Etidronate, alendronate, pamidronate, olpadronate, or amino-olpadronate (IG9402, a bisphosphonate that lacks antiresorptive activity) at 10-9 to 10-6 M prevented apoptosis of murine osteocytic MLO-Y4 cells, whether it was induced by etoposide, TNF-α, or the synthetic glucocorticoid dexamethasone. BPs also inhibited apoptosis of primary murine osteoblastic cells isolated from calvaria. Similar antiapoptotic effects on MLO-Y4 and osteoblastic cells were seen with nanomolar concns. of the peptide hormone calcitonin. The antiapoptotic effect of BPs and calcitonin was associated with a rapid increase in the phosphorylated fraction of extracellular signal regulated kinases (ERKs) and was blocked by specific inhibitors of ERK activation. Consistent with these in vitro results, alendronate abolished the increased prevalence of apoptosis in vertebral cancellous bone osteocytes and osteoblasts that follows prednisolone administration to mice. These results suggest that the therapeutic efficacy of BPs or calcitonin in diseases such as glucocorticoid-induced osteoporosis may be due, in part, to their ability to prevent osteocyte and osteoblast apoptosis.
CC 1-12 (Pharmacology)
Section cross-reference(s): 2
IT 2809-21-4 9007-12-9, Calcitonin 13598-36-2D, Phosphonic acid, alkylidinebis- derivs. 40391-99-9 63132-38-7, IG 9402 66376-36-1, Alendronate 121368-58-9, Olpadronate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin)
REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1986:430115 CAPLUS Full-text
DOCUMENT NUMBER: 105:30115
TITLE: Treatment of collagenous tissue
INVENTOR(S): Dewanjee, Mrinal Kanti
PATENT ASSIGNEE(S): Mayo Foundation, USA
SOURCE: Eur. Pat. Appl., 32 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 174737	A2	19860319	EP 1985-305681	19850809
EP 174737	A3	19870311		
R: BE, CH, DE, FR, GB, IT, LI, NL, SE				
DK 8503667	A	19860215	DK 1985-3667	19850813
AU 8546130	A	19860327	AU 1985-46130	19850813
AU 558688	B2	19870205		
JP 61137825	A	19860625	JP 1985-179218	19850814
PRIORITY APPLN. INFO.:			US 1984-640725 A	19840814

AB A process is given for the treatment of collagenous tissue to adapt it for use as a prosthetic implant and to promote the growth of endothelial cells thereon. The tissue is treated with at least 1 surfactant to remove deleterious material and open up the fibrous structure of the collagenous tissue, washed, fixed with glutaraldehyde, and the glutaraldehyde-fixed tissue is treated with a calcification-inhibiting agent, an agent that inhibits infiltration and attack by phagocytic cells and/or an agent that inhibits infection; and then the resulting matrix is treated with a reducing agent to stabilize the bonding of the agents and glutaraldehyde to the tissue. Thus, calf pericardial tissue was kept in Triton X100 for 3 h, washed, placed in 0.5% glutaraldehyde in 0.05M acetate buffer (pH 5.5) for 3.5 h, rinsed, and immersed in 3-amino-1-hydroxypropane-1,1- diphosphonic acid (16 mg/mL) in 0.05M acetate buffer, for 2-3 h. After 3 added cycles of immersion in glutaraldehyde (12 h)/rinsing, the tissue was soaked in 5 mg $NaBH_4$/mL for 30 min, rinsed, and stored in 0.5% glutaraldehyde. When valves made of this tissue were implanted in calves, there was no calcification, and abundant endothelial cell growth was observed

IC ICM A61L027-00
ICS A01N001-02

CC 63-7 (Pharmaceuticals)

IT 59-05-2 61-24-5 151-21-3, biological studies 9005-65-6 9063-89-2 40391-99-9 63132-37-6 63132-38-7 79778-41-9 97815-71-9
RL: BIOL (Biological study)
(collagenous tissue treatment with, for transplants)

L41 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	1983:181876 CAPLUS Full-text
DOCUMENT NUMBER:	98:181876
TITLE:	Scale prevention with special reference to threshold treatment
AUTHOR(S):	Van Rosmalen, G. M.
CORPORATE SOURCE:	Dep. Chem., Delft Univ. Technol., Delft, 2628 RZ, Neth.
SOURCE:	Chemical Engineering Communications (1983), 20(3-4), 209-33 CODEN: CEGCAK; ISSN: 0098-6445
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Various chemical, phys., and mech. methods for preventing deposition of mineral scale are described. The suitability of the different methods, which largely depends on the specific features and requirements of the system involved, is discussed. Special emphasis is placed upon the threshold treatment, where the growth process is retarded by the addition of trace amts. of growth inhibitors. Growth expts. were performed on $BaSO_4$ and $CaSO_4.2H_2O$ seed crystals, suspended in a supersatd. solution with and without organic bisphosphonates as inhibitors. Two methods are selected for the anal. of the growth data. A degree of inhibition is defined to obtain a quant. description of the growth-inhibitor effect on the growth rate. The effect of the mol. structure of various bisphosphonates is shown. The effect of a bisphosphonate on the geometry of $CaSO_4.2H_2O$ crystals is illustrated.

CC 48-11 (Unit Operations and Processes)
Section cross-reference(s): 61
IT 2809-21-4 29712-28-5 51395-42-7 63132-38-7 63161-30-8
RL: USES (Uses)
(crystal growth rates of barium sulfate and calcium sulfate dihydrate in relation to)

L41 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1983:597742 CAPLUS Full-text
DOCUMENT NUMBER: 99:197742
TITLE: The influence of various phosphonates on the growth rate of barium sulfate crystals in suspension
AUTHOR(S): Van der Leeden, M. C.; Reedijk, J.; Van Rosmalen, G. M.
CORPORATE SOURCE: Dep. Chem., Delft Univ. Technol., Delft, 2628 RZ, Neth.
SOURCE: Estudios Geologicos (Madrid) (1982), 38(3-4), 279-87
CODEN: EGLMA9; ISSN: 0367-0449
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The growth of BaSO4 crystals on walls of petrochem. equipment can be slowed by phosphonates having dissociated PO32- groups and H-bonding groups, such as CO2H, OH, or/and NH3+ groups. HO2CCH2CH(CO2H)CH(PO3H2)2 [51395-42-7] and MeC(OH)(PO3H2)2 [2809-21-4] are especially effective.
CC 51-23 (Fossil Fuels, Derivatives, and Related Products)
IT 2809-21-4 29712-28-5 29712-30-9 32545-63-4 40391-99-9 51395-42-7 53818-08-9 63132-38-7 63161-30-8 73514-83-7
RL: USES (Uses)
(barium sulfate scale inhibitors, for petrochem. equipment)

L41 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1980:181274 CAPLUS Full-text
DOCUMENT NUMBER: 92:181274
TITLE: Synthesis of 2- and 3-substituted alkanediphosphonic acids
AUTHOR(S): Worms, K. H.; Blum, H.; Hempel, H. U.
CORPORATE SOURCE: Henkel KGaA, Duesseldorf, D-4000/1, Fed. Rep. Ger.
SOURCE: Zeitschrift fuer Anorganische und Allgemeine Chemie (1979), 457, 214-18
CODEN: ZAACAB; ISSN: 0044-2313
DOCUMENT TYPE: Journal
LANGUAGE: German
AB Approx. 15 title compds. were prepared by phosphonylation of, primarily, aminoalkanoic acids and aminoalkanonitriles. Thus, 1 mol H3PO3, 1 mol PCl3, 330 mL PhCl and 0.5 mol Et2N(CH2)2CO2H gave 57% Et2N(CH2)2C(OH)[P(O)(OH)2]2. Similarly prepared were Me2C(NH2)C(OH)[P(O)(OH)2]2, MeCH(NH2)CH2C(OH)[P(O)(OH)2]2, H2NCH2CH2C(OH)[P(O)(OH)2]2, and H2NCHPhCH2C(OH)[P(O)(OH)2]2. Phosphonylation of 0.25 mol H2NCH2CH2CN in 100 mL dioxane with 0.5 mol PBr3 followed by hydrolysis gave H2NCH2CH2C(NH2)[P(O)(OH)2]2. Similarly prepared, were MeCH(NH2)CH2C(NH2)[P(O)(OH)2]2, MeNHCH2CH2C(NH2)[P(O)(OH)2]2, and Me2NCH2CH2C(NH2)[P(O)(OH)2]2.
CC 29-7 (Organometallic and Organometalloidal Compounds)
IT 63132-38-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction with nitrous acid)

L41 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1977:468491 CAPLUS Full-text

DOCUMENT NUMBER: 87:68491
TITLE: 1-Hydroxy-3-aminoalkane-1,1-diphosphonic acids
INVENTOR(S): Blum, Helmut; Worms, Karl Heinz
PATENT ASSIGNEE(S): Henkel und Cie. G.m.b.H., Fed. Rep. Ger.
SOURCE: Ger. Offen., 13 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2534391	A1	19770217	DE 1975-2534391	19750801
DE 2534391	C2	19830113		
NL 7607703	A	19770203	NL 1976-7703	19760712
US 4054598	A	19771018	US 1976-705792	19760716
BE 844649	A1	19770131	BE 1976-169348	19760729
JP 52019628	A	19770215	JP 1976-91196	19760730
JP 59025798	B	19840621		
CH 599234	A5	19780531	CH 1976-9788	19760730
GB 1540238	A	19790207	GB 1976-31891	19760730
AT 349642	B	19790410	AT 1976-5633	19760730
AT 350161	B	19790510	AT 1976-5631	19760730
AT 7605631	A	19781015		
CH 620359	A5	19801128	CH 1976-9789	19760730

PRIORITY APPLN. INFO.: DE 1975-2534391 A 19750801
AB RCH2C(OH)[P(O)(OH)2]2 (I, R = Me2NCH2, Et2NCH2, H2NCHMe) were prepared e.g. by treating RCH2CO2H with H3PO3 and P trihalide. I complex with 710 to 2500 mg CaCO3/g I at pH 11.
IC C07F009-38
CC 29-7 (Organometallic and Organometalloidal Compounds)
IT 63132-38-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(diazotization and hydrolysis of)

L41 ANSWER 14 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1977:423490 CAPLUS Full-text
DOCUMENT NUMBER: 87:23490
TITLE: 1,3-Diaminoalkane-1,1-diphosphonic acids
INVENTOR(S): Blum, Helmut; Worms, Karl Heinz
PATENT ASSIGNEE(S): Henkel und Cie. G.m.b.H., Fed. Rep. Ger.
SOURCE: Ger. Offen., 14 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2534390	A1	19770217	DE 1975-2534390	19750801
DE 2534390	C2	19830113		
NL 7607702	A	19770203	NL 1976-7702	19760712
NL 186575	B	19900801		
NL 186575	C	19910102		
BE 844648	A1	19770131	BE 1976-169347	19760729
JP 52019627	A	19770215	JP 1976-91195	19760730
JP 59025797	B	19840621		
FR 2319645	A1	19770225	FR 1976-23296	19760730

CH 599233	A5	19780531	CH 1976-9786	19760730
AT 347591	B	19790110	AT 1976-5632	19760730
GB 1540239	A	19790207	GB 1976-31892	19760730
AT 350160	B	19790510	AT 1976-5630	19760730
AT 7605630	A	19781015		
CH 620358	A5	19801128	CH 1976-9787	19760730

PRIORITY APPLN. INFO.: DE 1975-2534390 A 19750801

AB RCH2C(NH2)[P(O)(OH)2]2 (I, R = Me2NCH2, MeNHCH2, H2NCH2, H2NCHMe) were prepared by treating RCH2CN with PBr3 and H2O. I complex 630->2500 mg CaCO3/g I at pH 11 and can be used for water softening and in the treatment of calcification disorders.

IC C07F009-38

CC 29-7 (Organometallic and Organometalloidal Compounds)
Section cross-reference(s): 61, 63

IT 63132-36-5P 63132-37-6P 63132-38-7P 63161-35-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and complexing properties of)

L41 ANSWER 15 OF 15 PHAR COPYRIGHT 2007 Informa UK Ltd on STN

AN 14466 PHAR

DN 025567

ED Entered STN: 23 Apr 2003
Last Updated on STN: 15 Dec 2003

CN lidadronate

CN IG-9402

CN Phosphonic acid, (1-amino-3-(dimethylamino)propylidene)bis- (CAS)

RN 63132-38-7

MF C5 H16 N2 O6 P2

MW 262.14

HAC 8

HD 6

LOGP -0.74

FRB 9

NCE Yes

STA Ceased

CO

Type	Company Name (Country)	Development Status
Originator	Gador (Argentina)	No Development Reported

PI WO 9702827

PRAI GB 19950707

SO Pharmaprojects. PJB Publications, T&F Informa UK Ltd, London

TX Lidadronate (IG-9402) was under development by Gador for the treatment of urolithiasis, osteoporosis, periodontal diseases and other bone disorders (Direct communication, Gador, 23 Jan 2001). It is orally-active, and inhibits glucocorticoid-induced osteocyte apoptosis (Direct communications, Gador, 25 Jan 1999 and 28 Jan 2002).

Preclinical

In vivo, it showed no interference with resorptive bone metabolism (Direct communication, Gador, 28 Jan 2002). Lidadronate and analogues are patented as selective modulators of osteoblast-osteocyte cells (Direct communication, Gador, 25 Jan 1999). Updated by JB on

19/2/2002.
DSTA World: No Development Reported
Argentina: Preclinical Licensing Availability Unknown
Australia: Licensing Availability Unknown
Austria: Licensing Availability Unknown
Belgium: Licensing Availability Unknown
Brazil: Licensing Availability Unknown
Canada: Licensing Availability Unknown
Chile: Licensing Availability Unknown
China: Licensing Availability Unknown
Colombia: Licensing Availability Unknown
Denmark: Licensing Availability Unknown
Finland: Licensing Availability Unknown
France: Licensing Availability Unknown
Germany: Licensing Availability Unknown
Greece: Licensing Availability Unknown
Hong Kong: Licensing Availability Unknown
India: Licensing Availability Unknown
Ireland: Licensing Availability Unknown
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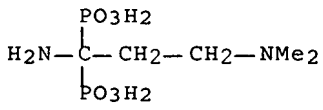
Japan: Licensing Availability Unknown
Luxembourg: Licensing Availability Unknown
Malaysia: Licensing Availability Unknown
Mexico: Licensing Availability Unknown
Netherlands: Licensing Availability Unknown
New Zealand: Licensing Availability Unknown
Norway: Licensing Availability Unknown
Peru: Licensing Availability Unknown
Philippines: Licensing Availability Unknown
Portugal: Licensing Availability Unknown
Russian Federation: Licensing Availability Unknown
South Africa: Licensing Availability Unknown
Korea, Republic of: Licensing Availability Unknown
Spain: Licensing Availability Unknown
Sweden: Licensing Availability Unknown
Switzerland: Licensing Availability Unknown
Thailand: Licensing Availability Unknown
Turkey: Licensing Availability Unknown
United Kingdom: Licensing Availability Unknown
United States: Licensing Availability Unknown
Venezuela: Licensing Availability Unknown
CC G4Z Urological
A1A Stomatological
M5A Osteoporosis treatment
CT Indication: Unspecified (No Development Reported)
GEN Target Gene: Unspecified
ORGM CH-SY (Chemical, synthetic)
RTE A-PO (Alimentary, po)
RDAT 20031211 RNTE ##Actual; No Development Reported
20010123 ##Estimated; Names Granted IG-9402
19970415 ##Estimated; New Product in Pharmaprojects
PHCD OSTEOBL-AG; Osteoblast stimulant; Physiological, Biochemical, Osteoblast stimulant; P-B-OSTEOBL-AG.
PHCD OSTEOBL-AN; Osteoblast inhibitor; P=Biochemical, OSTEO; P=B-OSTEOCL-AN.
PHCD APOP-AN; Apoptosis antagonist; Physiological, Biochemical, Apoptosis antagonist; General apoptosis antagonist; Apoptosis inhibitor; P-B-APOP-AN.
PHCD P; P-B; P-B-OSTEOBL; P-B-OSTEOBL-AG; P-OSTEOBL; P-OSTEOBL-AG; P-AG;

B; B-OSTEOBL; B-OSTEOBL-AG; B-AG; OSTEOBL; OSTEOBL-AG; P-B-AG; P=B; P=B-OSTEOCL; P=B-OSTEOCL-AN; P=B-AN; OSTEOCL; OSTEOCL-AN; P-B-APOP; P-B-APOP-AN; P-APOP; P-APOP-AN; P-AN; B-APOP; B-APOP-AN; B-AN; APOP; APOP-AN; P-B-AN.

LN

Therapy (CC)	Pharmacology (PHCD)	Status (DSTC)
G4Z	OSTEOBL-AG OSTEOBL-AN APOP-AN	N
A1A	OSTEOBL-AG OSTEOBL-AN APOP-AN	N
M5A	OSTEOBL-AG OSTEOBL-AN APOP-AN	N

LCDAT 20031211: IL : No development reported



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SEARCH HISTORY

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L1            1 SEA ABB=ON  US2003-619729/AP
                D SCAN

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L2                STR
L3            0 SEA SSS SAM L2

     FILE 'CAPLUS' ENTERED AT 15:19:07 ON 05 SEP 2007
                SEL RN L1
L4          220 SEA ABB=ON  ROLDAN E?/AU
L5         2651 SEA ABB=ON  PEREZ LLORET A?/AU OR PEREZ A?/AU OR LLORET A?/AU
L6          402 SEA ABB=ON  VAZQUEZ G?/AU
L7          198 SEA ABB=ON  BOLAND R?/AU
L8          138 SEA ABB=ON  PAPAPOULOS S?/AU
L9            1 SEA ABB=ON  L4 AND L5 AND L6 AND L7 AND L8
                D SCAN

     FILE 'REGISTRY' ENTERED AT 15:20:27 ON 05 SEP 2007
L10          21 SEA ABB=ON  (63132-38-7/BI OR 121368-58-9/BI OR 13598-36-2/BI
                OR 1406-16-2/BI OR 19356-17-3/BI OR 21829-25-4/BI OR 27121-73-9
                /BI OR 2809-21-4/BI OR 32222-06-3/BI OR 40391-99-9/BI OR
                471-34-1/BI OR 50-14-6/BI OR 52-53-9/BI OR 67-97-0/BI OR
                7440-70-2/BI OR 7693-13-2/BI OR 7782-41-4/BI OR 84449-90-1/BI
                OR 9001-86-9/BI OR 9002-64-6/BI OR 9002-72-6/BI)
                D SCAN
                E "PHOSPHONIC ACID, P,P'-(1-AMINO-3-(DIMETHYLAMINO)PROPYLIDENE)
L11           1 SEA ABB=ON  "PHOSPHONIC ACID, P,P'-(1-AMINO-3-(DIMETHYLAMINO)PR
                OPYLIDENE)BIS-"/CN
                D RN
                E 63132-38-7/CRN
L12           2 SEA ABB=ON  63132-38-7/CRN
L13           3 SEA ABB=ON  (L11 OR L12)
                D SCAN

     FILE 'ZCAPLUS' ENTERED AT 15:23:17 ON 05 SEP 2007
L14          24 SEA ABB=ON  L13

     FILE 'REGISTRY' ENTERED AT 15:23:27 ON 05 SEP 2007
L15               STR 63132-38-7
L16           0 SEA FAM SAM L15
L17          21 SEA FAM FUL L15 EXTEND
L18           3 SEA FAM FUL L15
                SAVE TEMP L18 ISS729FAM/A
L19           3 SEA ABB=ON  L18 AND L13
                D LC 1-3

     FILE 'REGISTRY' ENTERED AT 15:25:19 ON 05 SEP 2007
                SET TERMSET E#
                DEL SEL Y
                SEL L19 3 RN
L20           1 SEA ABB=ON  63132-38-7/RN
                SET TERMSET LOGIN
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     FILE 'PHAR' ENTERED AT 15:25:23 ON 05 SEP 2007
L21            1 SEA ABB=ON  L20
                 SET LINE 250
                 SET DETAIL OFF
                 SET LINE LOGIN
                 SET DETAIL LOGIN
                 D SCAN
                 D TRIAL

     FILE 'STNGUIDE' ENTERED AT 15:25:52 ON 05 SEP 2007

     FILE 'CAPLUS' ENTERED AT 15:27:36 ON 05 SEP 2007
L22           24 SEA ABB=ON  L13
L23           10 SEA ABB=ON  (L4 OR L5 OR L6 OR L7 OR L8 OR L1) AND L22

     FILE 'BIOSIS' ENTERED AT 15:28:13 ON 05 SEP 2007
L24          264 SEA ABB=ON  ROLDAN E?/AU
L25         2810 SEA ABB=ON  PEREZ LLORET A?/AU OR PEREZ A?/AU OR LLORET A?/AU
L26          332 SEA ABB=ON  VAZQUEZ G?/AU
L27          231 SEA ABB=ON  BOLAND R?/AU
L28          278 SEA ABB=ON  PAPAPOULOS S?/AU
L29            2 SEA ABB=ON  L13
L30            2 SEA ABB=ON  (L24 OR L25 OR L26 OR L27 OR L28) AND L29

     FILE 'DRUGU' ENTERED AT 15:29:06 ON 05 SEP 2007
L31           15 SEA ABB=ON  ROLDAN E?/AU
L32          224 SEA ABB=ON  PEREZ LLORET A?/AU OR PEREZ A?/AU OR LLORET A?/AU
L33           23 SEA ABB=ON  VAZQUEZ G?/AU
L34           22 SEA ABB=ON  BOLAND R?/AU
L35           43 SEA ABB=ON  PAPAPOULOS S?/AU
L36            1 SEA ABB=ON  L13
                 D TRIAL
L37            0 SEA ABB=ON  L36 AND LITERATURE/FS

     FILE 'CAPLUS' ENTERED AT 15:31:22 ON 05 SEP 2007
                 D QUE NOS L23

     FILE 'BIOSIS' ENTERED AT 15:31:23 ON 05 SEP 2007
                 D QUE NOS L30

     FILE 'CAPLUS, BIOSIS' ENTERED AT 15:31:27 ON 05 SEP 2007
L38           11 DUP REM L23 L30 (1 DUPLICATE REMOVED)
                      ANSWERS '1-10' FROM FILE CAPLUS
                      ANSWER '11' FROM FILE BIOSIS
                 D IBIB ABS HITSTR 1-11

     FILE 'REGISTRY' ENTERED AT 15:32:00 ON 05 SEP 2007
                 D STAT QUE L13
                 D IDE L13 1-3

     FILE 'CAPLUS' ENTERED AT 15:32:32 ON 05 SEP 2007
                 D QUE L22
L39           14 SEA ABB=ON  L22 NOT L23

     FILE 'BIOSIS' ENTERED AT 15:32:32 ON 05 SEP 2007
                 D QUE L29
L40            0 SEA ABB=ON  L29 NOT L30

     FILE 'PHAR' ENTERED AT 15:32:32 ON 05 SEP 2007
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                D QUE L21

     FILE 'CAPLUS, PHAR' ENTERED AT 15:32:38 ON 05 SEP 2007
L41           15 DUP REM L39 L21 (0 DUPLICATES REMOVED)
                     ANSWERS '1-14' FROM FILE CAPLUS
                     ANSWER '15' FROM FILE PHAR
                D IBIB ABS HITIND 1-14
                D ALL 15

     FILE 'HOME' ENTERED AT 15:33:00 ON 05 SEP 2007

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